SELECT
Selenium and Vitamin E
Cancer Prevention Trial

September 1, 2015

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5 of the SELECT protocol

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000B**, "Prevention of Cataract and Age-Related Macular Degeneration with Vitamin E and Selenium – SELECT Eye Endpoints (SEE), Phase III Ancillary to **S0000** - SELECT." Study Coordinators: Drs. W. Christen, R.J. Glynn and J.M. Gaziano.

STATUS NOTICE

Study Coordinator: William Christen, Sc.D.
Phone number: 617/278-0795
E-mail: wchristen@rics.bwh.harvard.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

PERMANENT CLOSURE

The study referenced above was permanently closed **effective July 31, 2015**, as the accrual has been met.

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
Elaine Armstrong, M.S. - Quality Assurance
William Christen, Sc.D. – SEE
Robert Glynn, Sc.D. - SEE

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

July 29, 2010

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5 of the SELECT protocol

FROM: Dana B. Sparks, M.A.T. – Director of Operations and Protocols

RE: **S0000B**, "Prevention of Cataract and Age-Related Macular Degeneration with Vitamin E and Selenium – SELECT Eye Endpoints (SEE), Phase III Ancillary to **S0000** - SELECT." Study Coordinators: Drs. W. Christen, R.J. Glynn and J.M. Gaziano.

STATUS NOTICE

Study Coordinator: William Christen, Sc.D.
Phone number: 617/278-0795
E-mail: wchristen@rics.bwh.harvard.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

RE-ACTIVATION

Effective July 29, 2010, the study referenced above is being re-opened for participation.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Elaine Armstrong, M.S. - Quality Assurance
William Christen, Sc.D. – SEE
Robert Glynn, Sc.D. - SEE

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

December 18, 2009

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5 of the SELECT protocol

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000B**, "Prevention of Cataract and Age-Related Macular Degeneration with Vitamin E and Selenium – SELECT Eye Endpoints (SEE), Phase III Ancillary to **S0000** - SELECT." Study Coordinators: Drs. W. Christen, R.J. Glynn and J.M. Gaziano.

STATUS NOTICE

Study Coordinator: William Christen, Sc.D.
Phone number: 617/278-0795
E-mail: : wchristen@rics.bwh.harvard.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( )Initial activation (should your institution choose to participate)
- ( )Increased risk to patient
- ( )Complete study redesign
- ( )Addition of tissue banking requirements
- ( )Study closure not built into study design

(√) Expedited review allowed

( ) No review required

TEMPORARY CLOSURE

The study referenced above will be temporarily closed, **effective December 31, 2009**, until further funding is identified.

Please attach this notice to the front of the protocol.

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Elaine Armstrong, M.S. - Quality Assurance
William Christen, Sc.D. - SEE

SELECT
Selenium and Vitamin E
Cancer Prevention Trial

October 19, 2009

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5 of the SELECT protocol

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000B**, "Prevention of Cataract and Age-Related Macular Degeneration with Vitamin E and Selenium – SELECT Eye Endpoints (SEE), Phase III Ancillary to **S0000** - SELECT."
Study Coordinators: Drs. W. Christen, R.J. Glynn and J.M. Gaziano.

STATUS NOTICE

Study Coordinator: William Christen, Sc.D.
Phone number: 617/278-0795
E-mail: wchristen@rics.bwh.harvard.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

PARTIAL CLOSURE REVISION

Effective November 1, 2009, accrual of new participants based solely on a diagnosis of cataract or a cataract extraction at follow-up will be closed as the study has reached the necessary accrual for this participant group.

The version date has been updated on the face page. This information is reflected in Section 5.2 (page 5), Section 7.3 (page 6) and in the Model Informed Consent Form (page 16). Additionally, as a clarification, in two places on page 15 the phrase "acute macular degeneration (AMD)" was changed to "age-related macular degeneration (AMD)".

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
Perrigo - Mark Mincey
Robert Glynn, Sc.D.
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Elaine Armstrong, M.S. - Quality Assurance
William Christen, Sc.D. – SEE
Robert Glynn, Sc.D. - SEE

Southwest
Oncology Group
A National Clinical Research Group

July 1, 2004

TO: Principal Investigators and Head Clinical Research Associates at Participating Study Centers and Study Sites listed in Appendix 19.5 of the SELECT protocol

FROM: Dana B. Sparks, M.A.T. - Protocol Product Line Manager

RE: **S0000B**, "Prevention of Cataract and Age-Related Macular Degeneration with Vitamin E and Selenium – SELECT Eye Endpoints (SEE), Phase III Ancillary to **S0000** - SELECT." Study Coordinators: Drs. W. Christen, R.J. Glynn and J.M. Gaziano.

STATUS NOTICE

Study Coordinator: William Christen, Sc.D.
Phone number: 617/278-0795
E-mail: wchristen@rics.bwh.harvard.edu

IRB Review Requirements

( ) Full board review required. Reason:
- (Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure not built into study design

(√) Expedited review allowed (due to minimal risk)

( ) No review required

ACTIVATION

The study referenced above will be officially activated for participant recruitment effective July 1, 2004.

If your institution intends to participate in this study, please obtain local IRB approval, document on the enclosed IRB Certification Form and forward a copy to the Operations Office by FAX at 210/677-0006.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: SELECT Statistical Center Staff - Phyllis Goodman, M.S.; Jo Ann Hartline, M.P.H., M.S.W.
SELECT Study Coordinators
Participating Cooperative Groups
Sabinsa - Vladimir Badmaev, M.D., Ph.D.
Roche - Vishwa Singh, Ph.D.
Nutricia - David Sullivan
Perrigo - Mark Mincey
VA Pharmacy Coordinating Center - Julia Vertrees, Pharm.D., B.C.P.P.
NCI - Frederick - Demetrius Albanes, M.D.
Elaine Armstrong, M.S. - Quality Assurance
William Christen, Sc.D. - SEE

HARVARD MEDICAL SCHOOL AND SOUTHWEST ONCOLOGY GROUP

PREVENTION OF CATARACT AND AGE-RELATED MACULAR DEGENERATION
WITH VITAMIN E AND SELENIUM - SELECT EYE ENDPOINTS (SEE)

PHASE III ANCILLARY TO **S0000** - SELECT

PARTICIPANTS: See Appendix Section 19.5 in main SELECT study (**S0000**)

STUDY COORDINATORS:

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mb

(Version Date 10/19/09)

1.0 OBJECTIVES

The primary and secondary objectives involve the main treatment effect of each study agent on AMD and cataract endpoints.

1.1 Primary Objectives

a. To test whether 400 mg of vitamin E reduces the risk of visually-significant AMD.

b. To test whether 200 µg of selenium reduces the risk of visually-significant AMD.

c. To test whether 400 mg of vitamin E reduces the risk of cataract.

d. To test whether 200 µg of selenium reduces the risk of cataract.

1.2 Secondary Objectives

a. To test whether 400 mg of vitamin E reduces the risk of advanced AMD.

b. To test whether 200 µg of selenium reduces the risk of advanced AMD.

c. To test whether 400 mg of vitamin E reduces the risk of cataract surgery and subtypes.

d. To test whether 200 µg of selenium reduces the risk of cataract surgery and subtypes.

2.0 BACKGROUND

Age-related macular degeneration (AMD) and cataract are two leading causes of visual impairment in older Americans. *(1)* AMD is the leading cause of visual impairment and blindness with an estimated 25% of people over 65 years showing some manifestation of AMD. *(1, 2)* More than 50% of the adult population in the U.S. aged 75 years and older suffers from visually significant cataract. *(1, 3, 4)* Treatment options for AMD and cataract are limited and not without important drawbacks. While laser photocoagulation, and more recently photodynamic therapy, have been shown to be of benefit for a minority of patients with advanced AMD, laser treatment merely delays subsequent vision loss, and the long-term effects of photodynamic therapy remain to be determined. *(5 - 9)* Cataract surgery accounts for a large proportion of Medicare expenditures. *(10)* Thus, the identification of inexpensive, safe strategies to prevent these common sources of ocular morbidity is of particular public health importance. *(1)*

Oxidative mechanisms are believed to contribute to the cumulative tissue damage observed in the aging retina and lens. *(11, 12)* There is also growing evidence that the development of AMD and cataract may be related to dietary habits, and in particular to the level of antioxidant nutrients contained in the diet. However, problems in altering dietary behavior and the need for life-long intervention make this preventive method difficult to implement. Instead, there has been increasing marketing and use of antioxidant supplements, including eye-specific preparations, despite the lack of convincing evidence supporting such usage. The recognition of the importance of oxidative mechanisms in AMD and cataract, together with the increasing consumption of vitamin supplements, led to the National Eye Institute-sponsored Age-Related Eye Disease Study (AREDS). AREDS tested in randomized trials the effects of daily doses of zinc (80 mg) and an antioxidant combination of vitamin E (400 IU), vitamin C (500 mg), and beta-carotene (15 mg) on the progression of AMD, and the effect of the antioxidant combination on the development and progression of lens opacities. The final randomized trial results for AMD, based on an average of 6.3 years of treatment and follow-up, indicated a benefit of zinc alone or in combination with antioxidant vitamins in delaying the progression to advanced AMD in persons at

high risk. *(13)* The data also suggested a risk reduction of 15 - 20% for those taking antioxidants alone. The results for cataract indicated no apparent effect of the antioxidant combination on development or progression of age-related lens opacities during the 6.3 years of treatment and follow-up. *(14)*

The findings in AREDS, particularly as they pertain to AMD, are important for the ocular health of the public and can be expected to generate a new wave of enthusiasm for supplementation with antioxidant nutrients. However, important questions remain. For example, the results for AMD in AREDS pertain to progression to advanced disease in persons in the 2 highest risk groups (persons with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye [AMD Categories 3 and 4]). Among the 2,180 participants in the 2 lower risk groups (persons with no AMD or mild or borderline age-related macular features including multiple small drusen, single or nonextensive intermediate drusen and/or pigment abnormalities in 1 or both eyes, and visual acuity of 20/32 or better in both eyes [AMD Categories 1 and 2]), only 20 cases of advanced AMD were noted by year 5. Thus, AREDS had limited power to assess the benefit of supplementation on progression to advanced AMD, or even to earlier stages of AMD, in persons at low risk. Such an evaluation in low risk individuals is needed, however, because early AMD can be associated with some degree of vision loss, but more importantly, is strongly predictive of subsequent development of advanced AMD. *(15, 16)* Regarding cataract, the AREDS investigators raise the possibility that for many participants, the intervention may have been initiated too late in the disease process, or was of inadequate duration, for it to be effective. Finally, for both AMD and cataract, the individual effects of vitamin E, vitamin C, and beta carotene in the antioxidant formulation could not be evaluated in AREDS, and thus require further study to clarify effects of individual nutrients.

Two antioxidant nutrients thought to offer protection from photo-oxidative damage are vitamin E and selenium. *(17)* Vitamin E is a powerful intracellular antioxidant that reduces lipid peroxidation, and selenium is an essential trace nutrient that is critical for the activity of glutathione peroxidase, an endogenous antioxidant enzyme that protects cellular molecules against oxidative damage. *(17 - 20)* Numerous basic research and observational epidemiologic studies suggest a plausible role for these nutrients, in particular vitamin E, in reducing risks of age-related eye disease. In addition, data indicate that activities of vitamin E and selenium (plus selenium-dependent glutathione peroxidase) are complementary and that the supplements could act synergistically to inhibit AMD and cataractogenesis. *(21 - 23)*

Inclusion of Minorities and Underserved/Uninsured

It is a standing policy of the Southwest Oncology Group to include eligible patients and/or participants of both sexes and all races and ethnicities in all Group clinical trials, except as restricted by specific disease site (e.g., prostate, gynecological). The proposed participant population for the full SELECT study (**S0000**) will consist of males, due to the specific disease site (prostate), and will include minority populations, including, but not limited to, African-Americans, Hispanics, Asian-Americans, as well as medically underserved populations. As African-American males are at higher risk for the development of prostate cancer, an attempt will be made to over-recruit this population through specific recruitment and adherence strategies. Previous minority accrual in Southwest Oncology Group genitourinary and cancer control studies in 1998 and other relevant studies is shown below:

ACCRUAL	Total	White	Black	Hispanic	Other
Committee (1998)					
GU	318	247 (77.7%)	57 (17.9%)	5 (1.6%)	9 (2.8%)
Cancer Control	532	447 (84.0%)	53 (10.0%)	13 (2.4%)	19 (3.6%)
PCPT (1994 - 1997)	18,882	17,272 (91.5%)	702 (3.7%)	497 (2.6%)	411 (2.2%)
Pivot Accrual (1994 - 1997)	578	379 (65.6%)	159 (27.5%)	27 (4.6%)	13 (2.2%)

3.0 DRUG INFORMATION

Drug information is not applicable to this study. This study will use the same agents as the main SELECT protocol (**S0000**).

4.0 STAGING CRITERIA

Staging Criteria are included in Appendix 19.2 of the main SELECT protocol (**S0000**) as a reference for staging participants who develop prostate cancer.

5.0 ELIGIBILITY CRITERIA

SELECT Participant No. _____

Participant's Initials (L,F,M) _____

5.1 The potential **S0000B** (SEE) participant must be a SELECT participant at the time of registration to SEE. Participants may be registered to SEE at any time after SELECT randomization. Participants are registered only after they report an eye event of interest (as outlined in Section 5.2 below).

5.2 The potential participant must report a diagnosis of age-related macular degeneration (AMD) at baseline (contact 010) or at follow-up, or a diagnosis of cataract or a cataract extraction at follow-up. (**Effective November 1, 2009 accrual of new participants based solely on a diagnosis of cataract or a cataract extraction at follow-up is closed.**)

A participant who reported a previous diagnosis of cataract at baseline (contact 010), then reports a cataract event (another cataract diagnosis or a cataract extraction) at follow-up, is not eligible.

A participant who reported a previous diagnosis of cataract at baseline (contact 010), then reports a diagnosis of AMD at follow-up is eligible.

5.3 Participants must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines before SEE procedures are initiated. Participants must have signed an applicable medical records release form and it must have been sent to Dr. William Christen at the SELECT Eye Endpoints (SEE) Center in Boston, MA by FAX (FAX #: 617/278-2030) immediately after registration to SEE.

5.4 At the time of participant registration, the treating institution's name and ID number must be provided to the Statistical Center in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

6.0 STRATIFICATION FACTORS

Stratification factors are not applicable to this study.

7.0 TREATMENT PLAN

All participants will receive treatment as outlined in **S0000**.

Please refer all questions regarding any procedures related to **S0000B** (SEE) to Dr. William Christen at 617/278-0795.

Detailed procedures for the Baseline Visit and Six Month and Annual Visits can be found in the **S0000B** (SEE) Study Manual, which is Appendix K of the SELECT Study Manual.

7.1 Baseline Visit

Participant information on previous diagnoses of cataract and AMD are collected as part of the baseline examination in SELECT. For SEE, medical record data will be collected (as described below) to confirm the baseline reports of AMD, but will not be collected for baseline reports of cataract or cataract surgery.

7.2 Six Month and Annual Visits

Participant reports of new diagnoses of cataract and AMD made since the start of **S0000B** (SEE) are collected at the SELECT Six Month and Annual Visits. This is accomplished through additional questions on Form 202 - Medical Events and on Form 208 - Prostate Cancer Follow-Up.

7.3 Medical Record Release

Participants who report a diagnosis of AMD at baseline, or a diagnosis of AMD at a SELECT Six Month or Annual Visit will be requested to complete a medical record release form on which they indicate the treating eye doctor(s) and provide written consent for the SELECT Eye Endpoints (SEE) Center to review the relevant medical records. The Study Site will register the participant to **S0000B** (SEE) via the SELECT workbench and then immediately fax the medical release form to the SELECT Eye Endpoints (SEE) Center in Boston, MA (FAX #: 617/278-2030). If the participant is unable to provide sufficient information about the event and the treating eye doctor(s) while at the Study Site, the participant will be asked to complete the form at home and return it to the Study Site in a self-addressed stamped envelope. The Study Site will register the participant to **S0000B** (SEE) and then immediately fax the form to the SEE Center. As an alternative to faxing the medical release form to the SEE Center, depending on Study Site local requirements, the Study Site may request the medical records from the ophthalmologist/optometrist, collect the detailed questionnaire and forward all materials obtained to the SEE Center (see Section 10.0).

7.4 Criteria for removal from protocol:

The participant may withdraw from the study at any time for any reason.

7.5 The participant will be followed as described in the main SELECT protocol (**S0000**).

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

Dose modifications will be performed as outlined in Section 8.0 of the main SELECT protocol (**S0000**).

9.0 STUDY CALENDAR

There are no scheduled study parameters to be followed for this study.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

All medical records obtained from the ophthalmologist/optometrist will be collected and reviewed at the SEE Center. Upon receipt of the medical record release form from the Study Site, the SEE Center will send a letter, a copy of the signed medical record release form, and a questionnaire to the ophthalmologist/optometrist asking about the reported diagnosis. Alternatively, the Study Site may request the medical records from the ophthalmologist/optometrist, collect the detailed questionnaire and forward all materials obtained to the SEE Center.

The AMD questionnaire will ask about (a) the date of initial diagnosis of AMD; (b) the best-corrected visual acuity at the time of diagnosis; (c) the date when visual acuity was first noted to be 20/30 or worse (if different from the date of initial diagnosis); (d) pathological findings observed (drusen, retinal pigment epithelium hypo/hyperpigmentation, geographic atrophy, retinal pigment epithelial detachment, subretinal neovascular membrane, or disciform scar) when AMD was first diagnosed; (e) pathological findings observed when visual acuity was first noted to be 20/30 or worse; (f) the date when exudative (wet) AMD was first noted (defined by presence of retinal pigment epithelium detachment, subretinal neovascular membrane, or disciform scar); (g) whether there are other ocular abnormalities which would explain or contribute to visual loss; (h) whether AMD, by itself, is significant enough to cause the vision to be reduced to 20/30 or worse; (i) whether laser treatment or photodynamic therapy was performed for AMD.

The cataract questionnaire will ask about (a) the date of initial diagnosis of cataract; (b) the best-corrected visual acuity at the time of diagnosis; (c) the date when visual acuity reached 20/30 or worse (if different from the date of initial diagnosis); (d) the date of cataract extraction; (e) whether there were other ocular abnormalities which could explain loss of visual acuity; (f) if other ocular abnormalities, whether cataract, by itself, is significant enough to cause the vision to be reduced to 20/30 or worse; (g) etiology of cataract (including age-related, traumatic, congenital, inflammatory, or surgery or steroid induced); (h) cataract type (nuclear, cortical, posterior subcapsular, other).

Ophthalmologists and optometrists may supply the requested information by providing photocopies of the relevant medical records instead of completing the forms.

Once obtained, the questionnaires and medical records will be reviewed by the Study Coordinator to determine their conformity with uniform diagnostic criteria.

Three categories of the AMD endpoint are defined: (a) AMD - self-report confirmed by medical record evidence of a diagnosis of AMD subsequent to randomization to SELECT (S0000); (b) AMD with vision loss - as in (a) but with vision loss to 20/30 or worse attributable to AMD (visually-significant AMD); (c) advanced AMD - as in (b), but including evidence of geographic atrophy or exudative disease.

The primary AMD endpoint in this eye study, visually-significant AMD, will, on average, represent a less severe stage of disease than cases meeting the criteria for advanced AMD in AREDS. In our other ongoing trials in men and women (Physicians' Health Study, Women's Health Study, Women's Antioxidant Cardiovascular Study) approximately 60 - 65% of cases meeting the criteria of vision loss to 20/30 or worse attributable to AMD are characterized by early signs of AMD only (i.e. some combination of drusen and/or retinal pigment epithelium changes). Thus, the primary AMD endpoint of visually-significant AMD will provide a meaningful test of whether antioxidant vitamins can be effective in lowering risks of earlier stages of AMD. In secondary analyses, we propose to examine whether the study agents reduce the risk of advanced AMD (cases with evidence of geographic atrophy or exudative disease) as well as total AMD including cases with and without vision loss.

Two cataract endpoints are defined: (a) cataract - self-report confirmed by medical record evidence of a diagnosis of age-related cataract subsequent to randomization to SELECT (S0000), with best-corrected visual acuity of 20/30 or worse due to cataract; (b) extraction - surgical removal of an incident cataract.

The primary cataract endpoint in this eye study provides a meaningful test of whether antioxidant vitamins can be effective in lowering risks of visually significant lens opacities. In secondary analyses, we propose to examine whether the study agents reduce the risk of cataract surgery as well as subtypes.

11.0 STATISTICAL CONSIDERATIONS

11.1 **Power Estimates:**

In this section we have computed the statistical power of the trial to detect plausible effects of vitamin E and selenium on the primary endpoints of visually-significant AMD and cataract among the anticipated 32,400 randomized men. Power is estimated with length of follow-up at planned termination (median follow-up, 8.8 years). Estimates of power are based on a two-sided log-rank test comparing event times between treatment groups at the 0.05 significance level. We use the formulas provided by Lachin and Foulkes with the following assumptions:

a. For both primary endpoints of visually significant AMD and cataract, we have used the event rates in Physicians' Health Study I to calculate the number of cases expected at the end of the planned length of follow-up of 8.8 years (median).

b. We assume that the age distribution of all participants in SELECT at randomization will match the age distribution of the randomized participants during the first 5 months of the trial (July-December, 2001). Further, we assume that the percentages of participants within each 5-year age group who have visually significant AMD or cataract at randomization will match the corresponding observed percentages in Physicians' Health Study I.

c. Applying physician rates to the projected randomized sample in SELECT, we anticipate that at baseline, 30,250 men will be free of a diagnosis of cataract, and 31,580 men will be free of a diagnosis of AMD. Also based on physician rates and the projected age distribution of the SELECT population, we assume that the rate of visually-significant AMD in the placebo group will be 3 events per 1,000 person-years, and the rate of cataract in the placebo group will be 10 events per 1,000 person-years.

d. Study duration will be 10 years with a minimum of 7 years of treatment.

e. Based on experience with similar trials, we expect the combined loss to follow-up, from both death and drop-out, to be less than 5 per 100 person-years. This rate is used in power calculations.

For the primary endpoint of visually-significant AMD, the study will have good power (80% or greater) to detect an observed RR 0.80 at the end of the total planned follow-up (median, 8.8 years). For the primary endpoint of cataract, the study will have excellent power (90% or greater) to detect an observed RR as low as 0.85 at the end of the total planned follow-up.

Power (%) for the main effects of vitamin E and selenium on the primary endpoints of visually-significant AMD and cataract with total planned follow-up.

		Total Planned Follow-Up (8.8 Years Follow-Up)	
Observed RR	True RR (assuming 100%) compliance)	Visually-significant AMD	Cataract
0.85	0.79	54.4	92.0
0.80	0.72	79.9	99.6
0.75	0.66	94.4	> 99.9
0.70	0.59	99.1	> 99.9
0.65	0.52	99.9	> 99.9

11.2 **Secondary Comparisons:**

Concerning the secondary endpoint of advanced AMD, with total planned follow-up we expect to have good power (80% or greater) to detect a benefit of treatment of 30% or greater. For the secondary endpoints of total AMD (with or without vision loss) and cataract surgery, we expect to have excellent power (90% or greater) to detect a benefit of treatment as small as 20% at the end of total planned follow-up.

11.3 **Data Analysis Plan:**

The study design is a 2 x 2 factorial trial of selenium (200 µg daily) and vitamin E (400 mg daily). Because of the large sample size, randomization should virtually assure that both known and unknown confounding variables will be distributed evenly among the treatment groups. Any imbalances that may occur with respect to known risk factors for AMD and cataract, or any medical or ocular condition which would require more medical attention thus increasing the likelihood of a diagnosis of AMD or cataract, will be controlled for in subsequent analyses.

Primary analyses will examine the main treatment effects of each study agent, and thus will differ from the primary analyses in the main SELECT study. Analyses of the main treatment effects will be based on the intent-to-treat principle with participants classified according to their randomized treatment assignment. Initial analyses of the AMD and cataract endpoints will include simple contingency tables in which the rate of each endpoint in terms of number of events per person-year of observation among participants allocated to active treatment will be compared with the incidence among those allocated to its placebo. For example, the incidence rate of AMD over the period of follow-up among participants assigned to active vitamin E will be compared with the rate for participants assigned to vitamin E placebo, controlling by stratification for selenium assignment. Similar analyses will separately examine the effects of selenium on the incidence of AMD, as well as the effects of vitamin E and selenium on the incidence of cataract. In addition, Kaplan-Meier survival estimates, the logrank test, and proportional hazards regression models will be used to determine whether there is a difference in time to diagnosis of AMD or cataract. *(25 - 27)* We will test for possible interaction of study agents by including an interaction term in proportional hazards regression models. Because an extended exposure to the study agents may be required to observe an effect, analyses will also be conducted which exclude AMD or cataract that develop during

the early years after randomization. Proportional hazards regression models will be used to evaluate smoking as a modifier of effects on AMD and cataract, and to evaluate effect modification by other factors including baseline dietary levels of the study agents. Additional analyses will separately evaluate the effect of vitamin E and selenium on the incidence of cataract surgery and cataract subtypes, and the incidence of advanced AMD (geographic atrophy and exudative AMD) and total AMD (with or without vision loss).

The primary analyses will consider individuals, rather than eyes, as units of analyses. This is consistent with current practice for survival analysis of ophthalmic trials when the individual, rather than the eye, is the unit of randomization. Some increase in statistical power would likely be obtained by considering eyes as the units of observation. Rosner has described an approach for estimation of parameters in logistic regression models that accounts for the correlation in disease risk between fellow eyes. *(28)* We will apply this model of Rosner to estimate the cumulative risk of developing an outcome in one eye given the treatment status of the individual and accounting for other baseline predictors. An additional benefit of this approach is that it explicitly quantifies the odds of an outcome in an eye given the outcome status of the fellow eye.

12.0 DISCIPLINE REVIEW

Discipline review is not applicable to **S0000B** (SEE).

13.0 REGISTRATION GUIDELINES

Registration procedures are specified in the SELECT Study Manual.

14.0 DATA SUBMISSION SCHEDULE

Detailed data completion and submission procedures and schedule are found in the SELECT Study Manual.

15.0 SPECIAL INSTRUCTIONS

Special instructions are included in Section 15.0 of the main SELECT protocol (**S0000**).

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each investigational drug supplied for a study, drug disposition (drug receipt, dispensing, transfer or return) shall be maintained on the NCI Investigational Drug Accountability Record. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the Drug Accountability Record; the ID # and initials of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned to the NCI or transferred to another NCI-approved protocol. These Drug Accountability Records must be readily available for inspection and are open to FDA or NCI inspection at any time.

Adverse Experiences

Any adverse experience, if deemed drug related, must be reported to the Operations Office Adverse Drug Reaction (ADR) representative (210/677-8808) as outlined in the SELECT protocol.

17.0 BIBLIOGRAPHY

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18.0 MASTER FORMS SET

NOTE: All forms to be utilized for this study will be available via the SELECT Workbench at http://swog.org. Forms completion and submission guidelines are found in the SELECT Study Manual.

A copy of the Initial Model Informed Consent document for **S0000B** (SEE) is enclosed and must be reviewed and approved by the institutional IRB before placing a participant on study.

For IRB use only, not to be included in patient information.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Readability Statistics:	Flesch Reading Ease	54 (targeted above 55)
	Flesch-Kincaid Grade Level	9.0 (targeted below 8.5)

S0000B, "Prevention of Cataract and Age-Related Macular Degeneration With Vitamin E and Selenium - SELECT Eye Endpoints (SEE), Phase III Ancillary to **S0000** - SELECT"

You are being asked to take part in this research study (SELECT Eye Endpoints – SEE) because you are taking part in SELECT and because you have reported that you were diagnosed with age-related macular degeneration (AMD) or a cataract. *(10/19/09)* We are asking you to release medical records about your eye diagnosis.

WHY IS THIS STUDY BEING DONE?

The purpose of SELECT, in which you are taking part, is to see if there is a difference in finding prostate cancer between a group of healthy men who received selenium alone, vitamin E alone, selenium and vitamin E and placebo.

Age-related macular degeneration (AMD) and cataract are two leading causes of visual impairment in older Americans. *(10/19/09)* **AMD is a disease that affects your central vision, and is the leading cause of visual problems and blindness with about 25% of people over 65 years showing some AMD. Cataract is a clouding of the eye's lens that causes loss of vision. More than 50% of adults in the U.S. aged 75 years and older suffer from visually significant cataract. Some evidence suggests that the vitamins being studied in SELECT might prevent these eye problems. This study will look at this question in a large group of men already assigned to take one, both or neither of these vitamins (men in the SELECT study).**

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Taking part in this study is your choice. While all men in SELECT (about 32,400 men) will submit baseline information about cataracts and AMD, approximately 2,150 men may be asked to submit additional medical information about cataract (*the cataract eligibility criterion was closed effective 11/1/09*) and 820 men may be asked to submit additional medical information about AMD for this study. *(10/19/09)*

WHAT IS INVOLVED IN THE STUDY?

Information about your health including prior diagnoses of cataract and AMD is being collected as part of the SELECT study. Because you have been diagnosed to have an eye condition, we are asking you to release medical records related to your eye diagnosis (and contact information for your treating eye doctor) to Harvard Medical School (Dr. William Christen).

Dr. Christen will review your records and may contact your eye doctor to get additional details about your eye diagnosis.

HOW LONG WILL I BE IN THE STUDY?

Your decision to release medical records and information to contact your eye doctor for each applicable eye diagnosis will be the extent of your participation in this study.

WHAT ARE THE RISKS OF THE STUDY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

For more information about risks and side effects, ask the researcher or contact _____.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There is no guarantee that you will get any personal benefit from taking part in this study. The findings of this study may help in our understanding of cataract or AMD and may help other people with these diseases in the future.

WHAT OTHER OPTIONS ARE THERE?

If you choose not to take part in S0000B, (SEE) but remain in SELECT, you have these other options:

You are encouraged to have eye checkups by your eye doctor and to follow the treatment recommended by your eye doctor. Remember that if you choose to take vitamin supplements for your eyes, the supplements must not contain vitamin E or selenium if you are in SELECT. Please talk to your regular doctor about these and other options

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as: the National Cancer Institute, Harvard Medical School, the Food and Drug Administration, the National Eye Institute; the makers of vitamin E, selenium and placebo pills for the study, and the Southwest Oncology Group.

If we publish the information we learn from this study in a medical journal, you will not be identified by name or in any other way.

WHAT ARE THE COSTS?

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may decline taking part in SEE without any effect on your participation in SELECT.

A Data and Safety Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

The persons in charge of this study are Drs. William Christen and Robert Glynn of the Harvard Medical School.

For questions about the study, contact the researcher *NAME(S)* at *TELEPHONE NUMBER*.

For questions about your rights as a research participant, contact the *NAME OF CENTER* Institutional Review Board (which is a group of people who review the research to protect your rights) at *TELEPHONE NUMBER*. *[And, if available, list participant representative (or other individual who is not on the research team or IRB).]*

WHERE CAN I GET MORE INFORMATION?

[To IRB/Investigators: Attach information materials and checklist of attachments. Signature page should be at the end of package. You may also wish to include the following informational resources]

You may call the NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

Visit the NCI's Web site…
www.cancer.gov

Visit the National Eye Institutes Web sites…
www.nei.nih.gov/

Or Prevent Blindness America®..
www.preventblindness.org/eye_problems

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

SIGNATURE

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study, and that you have read and understood all the information on this form.
My consent to participate in SELECT has been provided in a separate document.

Participant _____ Date _____